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Plasma membrane-associated superstructure: Have we overlooked a new type of organelle in eukaryotic cells?

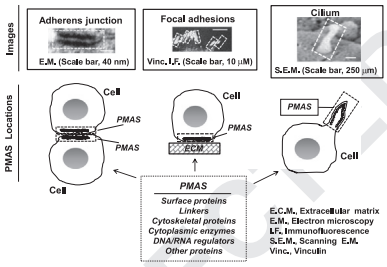
Q1 José Luis Rodríguez-Fernández *, Mario García de Lacoba

Q2 *Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas, Ramiro de Maeztu, 9, Madrid 28040, Spain*

HIGHLIGHTS

- We analyze a group of intriguing plasma membrane regions typical of eukaryotic cells.
- The importance of these regions for correct cell functioning is highlighted.
- We show that all these regions show a similar molecular structure and features.
- We suggest that these regions are the same organelle in different locations and cells.
- It is speculated that this special organelle could have appeared in eukaryotes.

GRAPHICAL ABSTRACT



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ABSTRACT

A variety of intriguing plasma membrane-associated regions, including *focal adhesions*, *adherens junctions*, *tight junctions*, *immunological synapses*, *neuromuscular junction* and the *primary cilium*, among many others, have been described in eukaryotic cells. Emphasizing their importance, alteration in their molecular structures induces or correlates with different pathologies. These regions display surface proteins connected to intracellular molecules, including cytoskeletal component, which maintain their cytoarchitecture, and signalling proteins, which regulate their organization and functions. Based on the molecular similarities and other common features observed, we suggest that, despite differences in external appearances, all these regions are just the same superstructure that appears in different locations and cells. We hypothesize that this superstructure represents an overlooked new type of organelle that we call plasma membrane-associated superstructure (PMAS). Therefore, we suggest that eukaryotic cells include classical organelles (e.g. mitochondria, Golgi and others) and also PMAS. We speculate that this new type of organelle might be an innovation associated to the emergence of eukaryotes. Finally we discuss the implications of the hypothesis proposed.

Nomina si nescis, perit et cognito rerum (You cannot perceive what it does not have a name)

Carl von Linné

1. Introduction

Over the last decades a variety of regions, constituted by specific plasma membrane proteins and associated cytoplasmic proteins located in the underlying cytoplasmic regions have been described in eukaryotic cells (Table 1). Among these regions are included *focal adhesions* (Burridge and Chrzanowska-Wodnicka, 1996; Wehrle-Haller and Imhof, 2002; Zamir and Geiger, 2001), *adherens junctions* (Kirkpatrick and Pfeifer, 1995; Yap et al., 1997),

* Corresponding author. Tel.: +34 91 837 3112.
E-mail address: rodrifer@cib.csic.es (J.L. Rodríguez-Fernández).

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desmosomes (Kirkpatrick and Pfeifer, 1995; Yap et al., 1997), *hemidesmosomes* (Borradori and Sonnenberg, 1996; Green and Jones, 1996), *tight junctions* (González-Mariscal et al., 2003; Sawada, 2013), *presynaptic densities* (Zhen and Jin, 2004; Ziv and Garner, 2004), *postsynaptic densities* (Choquet and Triller, 2013; Garner et al., 2000; Kennedy, 2000; Wilhelm et al., 2014), *neuromuscular junction* (Colledge and Froehner, 1998; Hemler, 1999), *podosomes* (Linder and Aepfelbacher, 2003), *immunological synapses* (Dustin and Colman, 2002; Huppa and Davis, 2003; Rodríguez-Fernández et al., 2010a, 2010b; Vicente-Manzanares et al., 2002), *uropod* (Fais and Malorni, 2003; Sanchez-Madrid and Serrador, 2009), *phagocytic cups* (Aderem and Underhill, 1999; Stuart and Ezekowitz, 2005; Underhill and Ozinsky, 2002), the *primary cilia* (Gerdes et al., 2009) and other regions described more recently (Barreiro et al., 2002; Sabatos et al., 2008) (Table 1). Sometimes these regions receive different names depending on the site where they were described, for instance *adherens junctions* are called '*zonulae adherens*' in polarized epithelia, '*fasciae adherens*' in cardiac muscle, and '*puncta adherens*' in mesenchymal and neural cells (Franke et al., 2009). Their widespread existence suggests that these superstructures are important for normal cell functioning.

Although other authors have also noted intriguing similarities among some of these regions – *immunological synapses* and *postsynaptic densities* (Labouesse and Georges-Labouesse, 2003), *focal adhesions* and muscle *adhesion structures* (Dustin and Colman, 2002), *immunological synapses* and *primary cilia* (Finetti et al., 2011; Stinchcombe and Griffiths, 2014) – a comparative study of them has not been performed until now. The information available in the scientific literature and in proteomic databases makes possible a first approach to this issue. Herein we have performed this analysis and find that all these regions share a similar organization. In this regard, all of them include sets of surface proteins that connect with a cytoskeletal network, which maintain the 3D-cytoarchitecture, and with intracellular signalling molecules (enzymes, linkers, DNA/RNA regulators and other molecules) that control their cytoarchitecture and specific functions. The analysis performed also suggests that, although until now each one of these regions has been considered as a different cellular entity, however, the molecular similarities observed support the notion that, despite differences in external appearances, all of them represent, in different cell types and locations, a novel type of cellular organelle that have been overlooked until now. We use the definition of organelle of the Encyclopedia Britannica (http://www.britannica.com/), which defines these entities as "any of the specialized structure within a cell that performs a specific function". We call this novel type of organelle plasma membrane-associated superstructure (PMAS), to distinguish it from classical membrane-bound intracellular organelles. Therefore, we suggest that eukaryotic cells includes classical organelles, like nucleus, mitochondria, Golgi, endoplasmic reticulum and other classical organelles, and also PMAS. Below we also speculate on the possible evolutionary origin of these novel organelles and discuss the implications of this hypothesis.

2. Plasma membrane-associated superstructures are observed at different membrane locations

Plasma membrane-associated superstructures have been observed using interference reflection microscopy (e.g. *focal adhesions* (Burridge and Chrzanowska-Wodnicka, 1996), electron microscopy (e.g. *desmosomes* (Dejana, 2004; Kirkpatrick and Pfeifer, 1995; Yap et al., 1997), *hemidesmosomes* (Borradori and Sonnenberg, 1996; Green and Jones, 1996; Jones et al., 1998), *tight junctions* (González-Mariscal et al., 2003; Sawada, 2013), *presynaptic densities* (Zhen and Jin, 2004; Ziv and Garner, 2004) *postsynaptic densities* (Garner et al., 2000; Kennedy, 2000) and *primary cilia* (Gerdes et al., 2009)) or by immunofluorescence, through the monitoring of plasma membrane or cytoskeletal protein components (e.g. *focal adhesions* (Burridge and Chrzanowska-Wodnicka, 1996; Wehrle-Haller and Imhof, 2002; Zamir and Geiger, 2001), *podosomes* (Linder and Aepfelbacher, 2003), *immunological*

Table 1
Examples of the membrane-associated superstructures and their postulated functions.

Region	Function/s	References
Focal adhesion	Adhesion to ECM, cell survival, growth and motility	Burridge and Chrzanowska-Wodnicka (1996), Zamir and Geiger (2001), Wehrle-Haller and Imhof (2002)
Podosome	Adhesion to ECM, motility, proteolysis of ECM	Linder and Aepfelbacher (2003)
Adherens junction	Cell–cell adhesion, cell sorting, cell polarity, cell differentiation, proliferation and motility, tissue integrity, tissue barrier formation	Kirkpatrick and Pfeifer (1995), Yap et al. (1997)
Desmosome[a]	Cell–cell adhesion and cell growth	Kirkpatrick and Pfeifer (1995), Yap et al. (1997), Dejana (2004)
Hemidesmosome	Adhesion to basal membrane	Borradori and Sonnenberg (1996), Green and Jones (1996)
Tight Junction	Cell–cell adhesion, paracellular diffusion	González-Mariscal et al. (2003),Sawada (2013)
Presynaptic density	Cell–cell adhesion, Neurotransmitter release	Zhen and Jin (2004), Ziv and Garner (2004)
Postsynaptic density	Cell–cell adhesion, post-synaptic response	Garner et al. (2000), Kennedy (2000), Choquetsend and Trillersend (2013), Wilhelm et al. (2014)
Neuromuscular junction	Transmission of impulse from motor neurons	Colledge and Froehner (1998), Hemler (1999)
Immunological synapse (T cell)[b]	T-cell activation	Dustin and Colman (2002),Rodríguez-Fernández et al. (2010a, 2010b)
Immunological synapse (DC)[c]	T-cell activation, Dendritic cell survival	Riol-Blanco et al. (2009), Rodríguez-Fernández et al. (2010b)
Uropod (T cell)	Anchoring of T-cells, presentation of growth factors, apoptosis	Fais and Malorni (2003), Sanchez-Madrid and Serrador (2009)
Phagocytic cup	Phagocytosis of particles	Aderem and Underhill (1999), Underhill and Ozinsky (2002), Stuart and Ezekowitz (2005)
Primary cilium	Cell growth, proliferation, autophagy, differentiation, morphology, mechanosensing	Gerdes et al. (2009), DeCaen et al. (2013), Delling et al. (2013)

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[a] *Desmosomes* can be classified in different types, depending on the intermediate filaments that are tethered in these areas. Keratin in epithelial tissues, desmin in myocardial and Purkinje fibre cells of the heart, and vimentin, in meningeal and follicular dendritic cells or cells in culture.
[b] Superstructure formed on the membrane of the T-cell.
[c] Superstructure formed on the membrane of the dendritic cell (DC). ECM; extracellular matrix.

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